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Cadmium: A Possible Etiological Factor in Peripheral Polyneuropathy

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Abstract: M.K. VIAENE, H. A. ROELS, J. LEENDERS, M. DE GROOF, L.J.V.C. SWERTS, D. LISON AND R. MASSCHELEIN. Cadmium: A Possible Etiological Factor in Peripheral Polyneuropathy. *Neurotoxicology* 20(1): 7-16, 1999. *Uncovering the exact cause of polyneuropathies seems to be impossible in up to 24% of the cases. Experimental studies have shown that cadmium (Cd), which is a well-known occupational and environmental hazard, can be a potent neurotoxicant for the peripheral nervous system. Moreover, Cd has a half-life of more than 15 years in humans. We hypothesize that older workers may be more susceptible to an increased Cd body burden, and may develop a peripheral polyneuropathy (PNP) over time. A blinded epidemiological survey was performed in 13 retired, long-term Cd-exposed workers and 19 age-matched controls. Historical Cd biomonitoring data were available over the last two decades. A neurological clinical examination, nerve conduction studies, and needle EMG were performed, and a standardized questionnaire was given to evaluate polyneuropathy complaints. If two of the following four criteria, i.e. complaints of polyneuropathy, neurophysiological changes compatible with polyneuropathy, distal symmetrical areflexia, or distal symmetrical anesthesia for vibration sense, temperature or blunt-sharp discrimination were present, the diagnosis of PNP was made. Two (11%) of the control and seven (54%) of the retired Cd workers met the PNP criteria OR: 9.92 (95%CI 1.60-61.6), Fisher exact test p=0.015. The existence of a polyneuropathy was related to the level of the Cd body burden as reflected by urinary Cd multiple logistic regression p=0.016, OR=1.26, (95%CI, 1.04-1.51), but not to blood lead (p=0.352). Our findings favour the hypothesis of a promoting role of increased cadmium body burden in the development of PNP at older age.* © *1999 Intox Press, Inc.*

Key Words: **Cadmium, Neurotoxicity, Polyneuropathy, Aging, Health Risk**

INTRODUCTION

Peripheral polyneurpathy (PNP) can be a severely invalidating disease and refers to the clinical syndrome produced by widespread involvement of the peripheral nerves with resulting loss of muscle stretch reflexes, impairment of sensation, muscle wasting and weakness. Uncovering the exact cause of polyneuropathies seems to be impossible in up to 24% of the cases (Dyck *et al.*, 1991; Lin *et al.*, 1993; Mcleod *et al.*, 1984; Swash and Schwartz, 1988). This implies that the potential contribution of some genetic factors, inflammatory or toxic events, which are not uncommon, could be of etiologic relevance for the development of PNP. Previously, several neurotoxic compounds in industrial settings have been associated with the development of PNP (e.g. lead, n-hexane, CS_2...). Cadmium (Cd) is a cumulative toxicant with a very long half-life in humans (> 15 years), which is known as an occupational hazard mainly for lung, kidney, and skeleton (Lauwerys, 1979). In 1974, the National Institute of Occupational Safety and Health (NIOSH) estimated that 100,000 workers in the USA are potentially exposed to this

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metal (NIOSH, 1976). More recently, Cd became also known as an environmental pollutant that may jeopardize public health (WHO, 1992). In 1979, it was estimated that in the USA between 2000-5000 metric tons of this toxic metal entered the environment each year (EPA, 1979).

It has been demonstrated many times by experimental studies that Cd^{2+} has major neurotoxic potentials (Babitch, 1988; Nagymajtényi *et al.*, 1997), however, there is a paucity of neurotoxic data in humans. This is probably due to early animal data, showing that only small amounts of cadmium could pass the blood-brain barrier (BBB) or blood-nerve barrier (BNB) in adult animals, even under chronic exposure conditions (Babitch, 1988). However, in humans many sites in the peripheral nervous system (PNS), and also in the central nervous system (CNS), are known to have less tight or even no barriers, e.g. the neuromuscular junction, the dorsal root ganglia, and the autonomic ganglia. Moreover, the effectiveness of the BBB and BNB can decline with aging (Jacobs, 1994) and the effect of Cd on the nervous system could very well exacerbate in older persons. This raised the hypothesis that older workers could be more susceptible to neurotoxic effects of an increased Cd body burden. The observation of a 47-year old patient, previously occupationally exposed to Cd for 18 years, prompted us to study the toxic potential of occupational Cd exposure on the human peripheral nervous system, and thus we conducted in 1995 a blinded cross-sectional study in a group of retired Cd workers and a matched control group.

SUBJECTS AND METHODS

Study Population

Our investigation was incorporated in on-going follow-up studies, that started in 1972, and focus on pulmonary and renal effects of Cd exposure (Lauwerys *et al.*, 1979; Roels *et al.*, 1989). This had major advantages: medical histories were well known so interfering disease could be excluded, and the participants were not especially alarmed on the possible neurotoxic risk of their occupational exposure, because it had never been an issue in the health surveillance of the workers.

In 1995, the retired male work force of the Cd production facility in a large Belgian zinc smelter comprised 18 ex-Cd workers alive of whom 5 did not participate in the study: one refused and four were severely ill. Nineteen age-matched workers who had been employed in the same plant, but never in the Cd production facility, constituted the control group. The retired Cd workers aged 47 to 81 years, had been occupationally exposed from 12 to 36 years, and their Cd exposure had ceased 1 to 24 years ago. The control workers aged 48 to 77 years, and had never been occupationally exposed to Cd or lead (Pb). For the retired Cd workers, historical data on biomonitoring of Cd and Pb exposure were available for the past 23 years (1972-1995). In 1978 the body burden of the Cd workers in this plant was assessed by neutron activation analysis of Cd in the liver (Roels *et al.*, 1981); the 13 retired Cd workers had a mean liver Cd of 55 µg/g (range 9 to 145 µg/g). For purpose of comparison, 50-year old American male nonsmokers have on average 2.3 µg Cd/g in the liver (upper normal value about 6 µg/g; Ellis *et al.*, 1979). Although exposure to Cd was the predominant occupational hazard of these workers, a mild exposure to Pb could not always be excluded. Historical blood Pb concentration (BPb) were available for all Cd workers; the highest BPb concentrations (BPbmax) ever measured in each individual Cd worker ranged from 15.3 to 47.1 µg/dl and slightly exceeded 40 µg/dl in two workers only (i.e. 44.6 and 47.1 µg/dl).

Study Design

The participants were instructed not to tell nor give any hints about their occupational history to the blinded examiner (MKV). A questionnaire inquired about lifestyle, medical and occupational histories, and other leisure-time neurotoxic exposures, the usual number of alcohol-containing drinks on working days and in the weekends, and previous alcohol abuse (>35 alcohol-containing drinks/week). Anamnestic alcohol intake was checked by the measurement of serum γ-glutamyltranspeptidase (GGT). The medical history, the medical records, and routine blood and urine analyses (glycemia, liver enzymes, ionogram, dip-stick) did not show any interfering disease. GGT and creatinine in serum were measured with an automated analyser Hitachi 917 (Boehringer, Mannheim, Germany). Creatinine concentration in the urine was determined using a Technicon RA-1000 (Tarrytown, USA). Cd and Pb in blood and Cd in urine were measured at the time of the study (1995) by electrothermal atomic absorption spectrometry as described previously (Roels *et al.*, 1978; 1991).

Questionnaire on Peripheral and Autonomic Nervous System

A PNP questionnaire comprising 14 questions concerning sensorimotor peripheral function was applied to each participant (difficulties performing fine

movements with the hands, difficulties performing movements requiring strength, muscle cramps, difficulties climbing stairs, unsteady gait, increased incidence of staggering, tingling sensations in fingers, tingling sensations in feet, burning pain in hands, burning pain in feet, hypoesthesia in hands, hypoesthesia in feet, feelings of "heaviness" in the legs, not feeling small injuries in feet or hands). In addition, five questions about dysfunction of the autonomic nervous system (ANS) were given (abnormal sweating, dizziness when getting up, palpitations, increased incidence of diarrhoea, increased incidence of constipation). Symptoms were scored on a 1 to 4 point scale (1=not, 2=sometimes, 3=often and 4=always having this symptom or complaint). The sum of scores for either the PNP or the ANS questions was calculated for each individual and devided by the number of questions. A mean score ≤ 2.0 (indicating that the subject reported usually "not" or "sometimes") was coded as 0 and a mean score > 2.0 (indicating that the subject reported "often" or "always") was coded as 1. The questionnaire was checked by an independent interviewer on missing data.

Neurological Examination

A standardized neurological clinical examination was performed, comprising general inspection, blood pressure after 5 minutes lying down and immediately after standing up (difference in systolic blood pressure, ΔSBP), tonus in upper and lower extremities, proximal and distal tendon reflexes, vibration sense (126 Hz tuning fork), temperature discrimination (Minnesota disks), blunt-sharp discrimination (Neurotip®), and motor function. Distal symmetrical paresis, distal symmetrical areflexia, and distal symmetrical anesthesia for temperature discrimination, blunt-sharp discrimination or vibration in both legs at least, were taken as positive clinical signs of a PNP.

Neurophysiological Measurements

Neurophysiological examinations were chosen according to suggestions made in the literature for epidemiological studies on diabetic polyneuropathy (Feldman *et al.*, 1994; Valk *et al.*, 1992; Veves *et al.*, 1995) and also according to the animal data which indicated autonomic and sensorial axonal damage and a possibility of Cd accumulation in the sciatic nerve (Arvidson and Tjälve, 1986). The neurophysiological signals were recorded with the limb temperature maintained between 32-34°C after pre-heating, using an infrared heater and a skin thermometer (COMARK 9001). Recordings were made with a DANTEC CANTATA EMG system, applying 1.2 times supra-maximal stimulation. First, sympathic skin response (SSR) amplitude and latency were elicited and recorded as described by Knezevic and Bajada (1985). The conventional motor nerve conduction velocities (MCV) were recorded in the peroneal nerve on both sides. Distal latency, response amplitudes (CMAP) and F wave latencies (best result of 16 stimulations) were recorded in the peroneal and tibial nerve on both sides and the median nerve on the right side. The conventional sensory nerve conduction velocity (SCV) and response amplitude (SNAP) were recorded in the sural nerve on the right side. The stimulations and recordings were done with surface electrodes as described by Shin J. Oh (1993) and the results were compared with published normal data (Oh, 1993). Needle EMG was performed in the short extensor muscle of the great toe of the right foot and in the first dorsal interosseous muscle of the right hand, using disposable bipolar concentric needle electrodes (DANTEC 0.45x30mm). With regard to the mean age of the study group, the neurophysiological outcomes were considered compatible with PNP if there was enough evidence of peripheral neuronal dysfunction: the CMAP, or SNAP, or conduction velocity had to be pathologically decreased in at least two of the three tested members and should be accompanied with reinervation signs in both distal muscles on needle EMG (poor recruitment, increased amplitude, duration and polyphasia of the motor unit potentials). Active denervation signs (fibrillation potentials and/or positive sharp waves) on needle EMG in both the short extensor muscle of the great toe and first dorsal interosseous muscle were also regarded as indicative for a PNP.

PNP Diagnosis

Based on suggestions made for epidemiological studies (Feldman *et al.*, 1994; Valk *et al.*, 1992; Veves *et al.*, 1995), the diagnosis of PNP was made if two of the following four criteria were present: i) complaints of polyneuropathy, ii) neurophysiological changes compatible with polyneuropathy, iii) distal symmetrical areflexia, or iv) distal symmetrical anesthesia for vibration sense, temperature or blunt-sharp discrimination. The subjects were assigned either to the category with PNP (coded 1) or without PNP (coded 0).

Statistics

Statistical analysis was done with SPSS software. Fisher exact test (two-tailed) was used, and the odds ratio (OR) and its 95% confidence interval (95%CI) were

calculated to assess differences between control and exposed workers as to the number of pathologic clinical signs, PNS complaint score, and ANS complaint score, and the number of PNP cases. Student's *t* test (two-tailed) was used to compare group differences in blood pressure change ΔSBP) and neurophysiological results. When needed log-normal transformation was performed (SSR amplitude, SCV).

For statistical analysis of CMAP and F waves, the mean result of the bilateral measurements was used, as the results of the statistical analysis did not show any significant difference when either mean results or unilateral measurements were used. The intra-individual correlations of the bilateral neurophysiological data were high ($0.74 \leq r \leq 0.92$, $p \leq 0.001$).

Outcome variables which were significantly different between the two groups, were subjected to multiple logistic regression analysis (dichotomous variables) or multiple linear regression, with either the highest urinary Cd concentration measured during work (cd-u WORK), or the urinary Cd concentration one to two years after exposure had ceased (cd-u BURDEN), or BPbmax as independent variables. For the control group, current Cd concentrations in urine and BPb were used because historical Cd and Pb biomonitoring data were not available for all the control subjects. Models were built up with the forced-entry method by introducing one of the exposure indices together with serum creatinine (mg/dl), alcohol use (drinks/week), history of alcohol abuse (0/1), and age (years) as covariates. For multiple linear regression analysis of the proximal conduction measurements (F wave responses), body size was considered as an additional covariate. In multiple logistic regression, odds ratio (OR) for each unit change in the exposure indices was calculated as described by Hosmer and Lemeshow (1989). P-values of 0.05 or less were regarded as statistically significant.

RESULTS

Group Characteristics

The characteristics of the control and Cd-retired groups at the time of the neurological examination are summarized in Table 1. Both groups are well-matched for age, height, and alcohol consumption. The duration of the cadmium exposure was 23.3 years on average. Serum creatinine concentration was normal (<1.60 mg/dl) in all subjects, except in two retired Cd workers (i.e. 2.51 and 2.95 mg/dl). The group means of serum creatinine are not significantly different between control and retired Cd workers. GGT levels in serum were all normal (≤45 IU/l). A previous history of alcohol abuse (>35 drinks/week) was reported in one exposed and three control subjects which may explain the higher GGT values in serum of the control group. The current lead exposure in both groups as reflected by the blood lead concentration is low and during the last 10 years BPb remained below 20 µg/dl. Apart from a slight occupational lead exposure in the past for some Cd-retired workers and a low-level environmental lead exposure in the controls, the questionnaire did not reveal any occupational or significant occasional (leisure time, home) exposure to

TABLE 1. Characteristics of the Control and Retired Cd Workers at the Time of the Neurological Examination in 1995.

	Control Group (n=19)		Exposed Group (n=13)	
	MEAN ± SD	(Range)	MEAN ± SD	(Range)
Age	61.0 ± 7.5	(48-77)	66.5 ± 8.6	(47-81)
Years of Cd exposure	-	-	23.3 ± 8.3	(12-36)
Years of removal from Cd exposure	-	-	16.1 ± 7.7	(1-24)
Height (cm)	173.0 ± 5.9	(158-182)	172.1 ± 6.4	(158-185)
cd in urine (µg/g creatinine.)	1.05 ± 0.50	(0.35-1.96)	8.78 ± 3.80	(3.8-16.6)
cd in blood (µg/dl)	0.10 ± 0.05	(0.04-0.22)	0.60 ± 0.28	(0.18-1.15)
Serum creatinine (mg/dl)	1.16 ± 0.16	(0.97-1.53)	1.37 ± 0.64	(0.82-2.95)
Serum GGT [a] (IU/l)	25.3 ± 11.7	(9-45)	16.8 ± 6.5	(3-26)
Alcohol (drinks/week)	2.9 ± 2.2	(0-8)	2.0 ± 2.1	(0-7)
Pb in blood (µg/dl)	8.0 ± 3.6	(1.7-16.4)	9.3 ± 3.9	(3.8-16.3)

[a] GGT= -glutamyltranspeptidase activity (normal ≤45 IU/l).

TABLE 2. Individual Data of Controls (C) and Retired Cd Workers (R) with Regard to Polyneuropathy (PNP) Associated with Occupational Cadmium Exposure.

C/R	Age	AA [a]	Creat.[b]	BPb [c]	Cd-U		Neurological Findings				Diagnosis
		(0/1)	(mg/dl)	(µ/dl)	(µg/g creatinine)		PNP compl.[g]	Anesthesia.[h]	Areflexia [i]	EMG [j]	of PNP[k]
C	64	0	1.05	5.2	0.57 [d]		-	+	+	-	+
C	61	0	1.08	6.0	1.04		-	-	+	+	+
C	77	0	1.53	11.6	1.14		-	-	-	+	-
C	70	0	1.38	4.9	0.81		-	-	-	-	-
C	69	0	0.97	13.1	1.35		-	-	-	+	-
C	67	0	1.08	11.3	1.96		-	-	-	-	-
C	65	0	1.28	5.7	1.19		-	-	-	-	-
C	63	0	1.17	4.1	0.83		-	-	-	-	-
C	63	0	1.18	10.7	0.92		-	-	-	+	-
C	56	1	1.04	10.2	1.74		-	-	-	-	-
C	61	0	1.08	6.8	0.72		-	-	-	-	-
C	60	0	1.10	7.1	1.81		-	-	-	-	-
C	59	0	1.13	9.3	0.49		-	-	-	-	-
C	59	1	0.98	9.2	1.02		-	-	-	-	-
C	59	0	1.15	16.4	1.24		-	-	-	-	-
C	53	0	1.05	1.7	0.35		-	-	-	-	-
C	49	1	1.23	7.1	1.75		-	-	-	-	-
C	49	0	1.07	4.9	0.63		-	-	-	-	-
C	48	0	1.06	5.7	0.37		-	-	-	-	-
					WORK [e]	BURDEN [f]					
R	47	0	0.90	22.3	20.6	8.4	+	-	-	+	+
R	58	0	0.95	17.6	24.0	16.4	-	+	-	+	+
R	62	0	1,06	15.3	11.2	8.2	+	+	-	-	+
R	71	1	1.00	24.0	15.5	7.0	-	-	+	+	+
R	73	0	1.28	25.6	18.9	8.2	+	-	+	+	+
R	76	0	2.51	35.3	25.4	23.5	+	-	+	+	+
R	81	0	0.82	31.0	37.0	12.5	-	+	-	+	+
R	62	0	2.95	47.1	24.7	15.0	-	-	-	+	-
R	65	0	1,13	38.4	38.4	14.9	+	-	-	-	-
R	68	0	1.16	37.8	18.0	8.3	-	-	+	-	-
R	65	0	1.09	15.6	22.1	12.6	-	-	-	-	-
R	69	0	1.53	31.1	19.1	10.1	-	+	-	-	-
R	72	0	1.41	44.6	9.8	9.8	-	-	-	-	-

[a] AA: alcohol abuse in the past (yes, 1; no, 0); current alcohol consumption was normal and all workers had normal serum GGT (≤45 IU/l).
[b] Creat.: serum creatinine at the time of neurological examination in 1995.
[c] BPb: control workers, current blood lead concentrations; retired Cd workers, highest blood lead concentrations ever measured during work.
[d,e,f]: [d]Current urinary Cd concentration at the time of the neurological examination in 1995; [e]WORK, highest urinary Cd concentration ever measured during working time; [f]BURDEN, urinary Cd concentration one to two years after cessation of exposure.
[g] PNP complaints: compatible with PNP if score of complaints exceeds 2 (coded as +).
[h] Anesthesia: compatible with PNP if a distal symmetrical anesthesia for blunt-sharp or temperature discrimination or vibration sense was present in both legs at least (coded as +).
[i] Areflexia: compatible with PNP if a distal symmetrical areflexia was present in both legs at least (coded as +).
[j] EMG: compatible with PNP if decreased CMAP or SNAP amplitude or conduction velocity slowing was present in at least two of the three tested members, together with reinervation signs in the distal muscles on needle EMG (coded as +).
[k] PNP: diagnosed as PNP (coded as +) if two of the neurological criteria were positive (see also Methods).

TABLE 3. Neurophysiological Findings in the Control and Retired Cd Workers.

	Controls (n=19)		Exposed (n=13)	
	Mean ± SD	(Range)	Mean ± SD	(Range)
CMAP peroneal nerve (mV)[a]	6.7 ± 2.8	(2.9-11.7)	4.4 ± 2.5*	(0.7-9.9)
CMAP tibial nerve (mV)[a]	10.0 ± 4.5	(3.3-17.0)	8.6 ± 4.7	(2.3-18.3)
CMAP median nerve (mV)	6.5 ± 3.1	(2.4-10.6)	7.8 ± 4.3	(1.5-12.4)
SNAP sural nerve (μV)	9.7 ± 3.8	(0.0-15.0)[b]	7.0 ± 5.0	(0.0-16.4)[b]
MCV peroneal nerve (m/sec)	44.2 ± 4.8	(37.3-54.8)	43.9 ± 4.3	(37.4-53.2)
SCV sural nerve (m/sec)	51.9 ± 5.9	(45.3-66.7)[b]	48.8 ± 16.3	(43.7-56.0)[b]
F wave peroneal nerve (msec)[a]	50.1 ± 5.9	(36.6-63.6)	52.7 ± 4.8	(46.8-62.4)
F wave tibial nerve (msec)[a]	52.2 ± 6.3	(41.6-59.2)	58.1 ± 5.3*	(46.8-66.8)
F wave median nerve (msec)	27.8 ± 1.5	(24.4-29.6)	28.4 ± 3.9	(22.8-36.8)
SSR latency (msec)	1789 ± 354	(1080-2320)	2034 ± 401(*)	(1360-3080)
SSR amplitude (μV)	464 ± 263	(80-1100)	301 ± 179	(120-630)

[a] Average of bilateral measurements.
[b] The SNAP and SCV of the sural nerve could not be elicited in 3 persons (1 control, 2 exposed). These data were left out for the statistical analysis.
* $p \leq 0.05$, (*) $0.05 < p \leq 0.10$ compared to controls (Student's *t* test).

known neurotoxicants. Although the Cd workers are retired from Cd exposure for 16.1 years on average, the mean concentration of Cd in urine and blood of this group is currently still 8 and 6 times higher respectively, than the mean values in the control group. In the retired Cd workers, Cd-U WORK (μg/g creatinine) (taken as an index of the highest level of cadmium exposure during work) was on average 21.9 ± SD 8.5 (range 9.8 to 38.4), and Cd-U BURDEN (μg/g creatinine) (taken as an index of Cd body burden 1 to 2 years after exposure had ceased), was 11.9 ± SD 4.6 (range 7.0 to 23.5).

Individual Data

Table 2 summarizes the most relevant individual data of the control and retired Cd workers with regard to age, alcohol abuse in the past, renal function (serum creatinine), lead exposure (blood lead), and exposure to cadmium (as reflected by urinary Cd) together with findings of the neurological examinations and PNP diagnosis.

ANS and PNP Questionnaire

The questionnaire for autonomic nervous system (ANS) complaints detected only one control and two exposed workers with complaints of ANS (p=0.55; OR=3.3, 95%CI 0.27-40.47). In contrast, the questionnaire of peripheral nervous system complaints identified five exposed workers with complaints of PNP against none in the control group (p=0.006; OR=12.5, 95%CI 1.7-92.9).

Neurological Examination

The standardized neurological examination revealed distal symmetrical areflexia in 4 (30.8%) of the exposed workers and 2 (10.3%) of the control workers (p=0.19; OR=3.8, 95%CI 0.6-24.8). Distal symmetrical anesthesia for at least one modality was present in 4 (30.8%) of the exposed workers and 1 (5.3%) of the control (p=0.13; OR=8.0, 95%CI 0.8-80.5). Nobody showed distal symmetrical paresis. The blood pressure measurements (in mmHg) in the supine position were not significantly different between control group (mean value ± SD: systole 136 ± 10, diastole 88 ± 9) and exposed group (mean ± SD: systole 145 ± 22, diastole 87 ± 11). The difference in systolic blood pressure (ΔSBP) between the supine and the upright position was more pronounced in the Cd group (mean ± SD: -10 ± 12, range -35 to +18) compared to the control group (+4 ± 10, range -19 to +17) (p<0.007).

Neurophysiological Measurements

The results of the neurophysiological measurements are summarized in Table 3. The amplitude of the CMAP of the peroneal nerve was significantly lower (p=0.022) in the exposed group compared to the controls, whereas the CMAP of the tibial and median nerves did not differ significantly between controls and exposed. The sural SNAP (p=0.103), the SCV (p=0.153), and the mean SSR amplitude (p=0.158) of the exposed group were up to 35% lower than that of the control group, but did not reach statistical significance due to the wide range of the results

TABLE 4. Multiple Logistic Regression of PNP Complaints and PNP Diagnosis in the Controls and Retired Cd Workers Combined.

	Cd-U BURDEN [a]		Cd-U WORK [a]		BPbmax [a]	
	p	OR (95% CI) [b]	p	OR (95% CI)[b]	p	OR (95% CI)[a]
PNP complaints	0.038	1.29 (1.02-1.65)	0.046	1.13 (1.00-1.27)		NS
Diagnosis of PNP [c]	0.016	1.26 (1.04-1.51)	0.028	1.11 (1.01-1.21)		NS

[a] Independent variables introduced separately in the model together with age, alcohol use, history of alcohol abuse, and serum creatinine. For details, see Subjects and Methods.
[b] Odds ratio and 95% confidence interval.
[c] For details see Methods.
NS: p>0.05.

and the small size of the study group. The SSR latency in the exposed group showed a borderline significant increase (p=0.079). With regard to the F wave latencies, only those in the tibial nerve were significantly (p=0.006) higher in the exposed workers compared to the controls. In two exposed workers, active denervation signs on needle EMG were present, whereas none in the controls (Fisher exact test, p=0.157).

PNP Diagnosis

On the basis of the criteria defined in the methods, PNP was diagnosed more frequently in the retired Cd workers (7/13, 54%) than in the controls (2/19, 11%) (OR=9.92; 95%CI, 1.6-61.6; Fisher exact test, p=0.015). In the exposed group three of the seven workers with a positive neurophysiological examination had an excess of PNP complaints and five had impaired sensory testing or areflexia. This was less pronounced in the control group (no excess of complaints and only one person with clinical signs). Only one exposed person had an excess of PNP complaints without EMG or clinical signs of a PNP (see Table 2).

Dose-Effect / Dose-Response Relationship

In multiple linear regression analyses, the ΔSBP and the F wave latency in the tibial nerve were significantly related to cd-U BURDEN (r^2=0.19, p=0.018; r^2=0.20, p=0.013) and borderline to cd-U WORK (r^2=0.13, p=0.055; r^2=0.13, p=0.063). BPbmax was only significantly related to the F wave latencies in the tibial nerve (r^2=0.17, p=0.023). No relation was found between cd-U BURDEN, cd-U WORK, or BPbmax and the amplitude of the peroneal CMAP (p>0.10). Of all covariates in these multiple linear regression analyses, only the body size explained a significant part of the F wave results (p<0.05).

Table 4 summarizes the results of the multiple logistic regression analyses. Each Cd exposure index was significantly associated with complaints of PNP and the diagnosis of a PNP (p<0.05). The slight lead exposure in the retired Cd workers, as reflected by the highest blood lead concentration ever measured (BPbmax), did not explain the prevalence of PNP in this study population (p=0.35). None of the covariates did contribute in the multiple logistic regression model (age, p=0.21; alcohol consumption, p=0.38; serum creatinine, p=0.92). These findings are supported by the fact that the mean BPbmax in the seven retired Cd workers with PNP was lower than in the six without PNP [mean ± SD (range): BPbmax (μg/dl), 24.4 ± 7.0 (15.3-35.3) vs. 35.8 ± 11.4 (15.6-47.1), (*t* test, p=0.05] and that serum creatinine and age did not differ significantly between both groups [mean ± SD (range): serum creatinine (mg/dl), 1.22 ± 0.59 (0.82-2.51) vs. 1.55 ± 0.71 (1.09-2.95); age, 66.9 ± 11.8 (47-81) vs. 66.8 ± 3.5 (62-72)].

DISCUSSION

Uncovering the cause of a polyneuropathy is often unrewarding, especially in axonal sensorimotor neuropathies developing at the age of 40 or later. Many exogenic (e.g. alcohol, lead) and endogenic (e.g. diabetes) factors have been found to be important in the genesis of this disease (Swash and Schwartz, 1988). Data concerning human cadmium neurotoxicity are sparse, but indicate possible peripheral nervous system toxicity. Symptoms of fatigue, muscle weakness, syncope, and anosmia were reported in patients or workers exposed to Cd (Baader, 1952; Bar-Sela *et al.*, 1992; Dunphy, 1967; Prodan, 1932). In addition, an Eastern-European study demonstrated clinical evidence for PNP positively associated with urinary cadmium concentrations and exposure duration (Musiol *et al.*, 1981). This group of Cd-exposed workers, which was similar to our group as to exposure levels and duration, showed a comparable high prevalence of PNP (65%). In a case-report, a minor axonal sensory PNP in a 54-year old man probably related to Cd contamination of drinking water (Blum *et al.*, 1989) has been described, but the effect of concomitant high Pb exposure could not be

ruled out. The only autopsy report of a long-term Cd-exposed worker who died from lung emphysema due to cadmium revealed widespread degenerative changes in the autonomic abdominal intramural and bronchial wall plexus (Baader, 1952).

The major route of occupational cadmium intoxication is inhalation of cadmium fumes or dust. Other sources of cadmium exposure are cigarette smoking, and Cd-contaminated food and water. After absorption, the pool of free cadmium in blood is rapidly bound to metallothionein of which the synthesis in the liver is stimulated by Cd. In animal studies it has been shown that this Cd-metallothionein complex does not cross the BBB and BNB. This is certainly true in short-term exposure conditions (Babitch, 1988), but might be different in long-term exposure situations, especially when combined with the consumption of alcohol (Pal *et al.*, 1993). Nevertheless, cadmium has been shown to accumulate in some parts of the central and peripheral nervous tissue lacking a tight BBB, such as in the pituitary gland, the pineal gland, the olfactory bulb, the sensory and autonomic ganglia (Babitch, 1988), but it has also been shown to accumulate in the sciatic nerve, which has a tight BNB (Arvidson and Tjälve, 1986). In experimental studies axonal but also demyelinisating effects have been associated with Cd toxicity. Sato *et al.* (1978) demonstrated that exposure of rats to low concentrations of Cd^{2+} in drinking water for 18-31 months resulted in a slight reduction in the number of dorsal root ganglia and induced a segmental demyelinisation beginning from the nodes of Ranvier. Disruption of vascular membranes (Gabbiani *et al.*, 1967), increased oxidative stress (Ali *et al.*, 1993; Pal *et al.*, 1993), or interference of Cd^{2+} with Schwann cell metabolism (Baader, 1952) have been suggested as causes of this nerve damage.

Taken together, those findings support the viewpoint that the PNS is most likely the first target in the nervous system. The results of our study give a strong indication that cadmium has a major peripheral neurotoxic potential in humans, since in this group of retired Cd workers an increased risk of developing a PNP was found (OR=9.91; 95%CI 1.6-61.6). This risk is best related to the level of urinary cadmium after exposure had ceased.

In this study, nerve conduction velocities were not more slowed compared to the decrease of the amplitudes of their compound muscular or sensory action potentials, which is more suggestive of axonal or neuronal damage than of demyelinisation. But it must be noted that the proximal conduction velocity (F waves) of the tibial nerve was significantly slowed while no effect on the CMAP could be detected. Therefore, a combination of demyelinisation and axonal damage, as has been described in animal studies (Sato *et al.*, 1978), may also be possible.

It could be argued that our findings are a consequence of minor impairments without clinical relevance which are frequently found on neurophysiological examination in older-age patients, as nerve conduction velocities, SNAPs and CMAPs decline especially after the age of 60 (Oh, 1993). Such preclinical findings were evidenced in 3 (15.8%) subjects of the control group. However, the neurophysiological deficits in the exposed workers tended to be worse: e.g. 2 (15.4%) had active denervation on needle-EMG and in 2 (15.4%) the SNAP was absent, versus 0 and 1 (5.3%) in the control group (see also Table 3). In addition, most of the exposed workers with neurophysiological deficits had clinical signs compatible with the PNP [5/7 (71.4%) compared to 1/4 (25%) in the control group]. This supports the finding that the exposed subjects had more PNP complaints than the control workers.

Occupational Cd exposure in most job-functions is usually accompanied with a slight Pb exposure. Although peripheral neuropathy is a well-documented effect of high protracted Pb exposure, lower exposures (BPb 30 to 40 µg/dl) may produce subclinical changes in nerve conduction velocities, especially in the median nerve (Davis and Svendsgaard, 1990). The group of retired Cd workers in the present study had experienced long-term high Cd exposures during their professional career, while their Pb exposures had been rather low. Only one of the neurophysiological parameters was related to Pb exposure (F wave latency of tibial nerve), but to a lesser extent compared to cadmium exposure. In addition, the retired Cd workers with PNP had significantly lower historical blood Pb levels than those without PNP, making it very unlikely that Pb would be involved in the neurotoxic mechanism. It also might be argued that the observed neurological effects were secondary to a reduced renal function. This hypothesis also seems unlikely because even the highest serum creatinine level in the retired Cd workers was only half the level which is considered to cause peripheral nervous system pathology (≥6 mg/dl) (Swash and Schwartz, 1988). Moreover, the retired Cd workers with a PNP had a slightly lower mean serum creatinine level compared to those without PNP. No relation was found between serum creatinine and the anamnestic, clinical, or neurophysiological variables, and adding this covariate to the regression models did not influence the relation with urinary cadmium.

CONCLUSION

Our findings favour the hypothesis of a promoting role of increased cadmium body burden in the development of PNP at older age (> 50 years). The present findings are consistent with the experimental data showing that Cd is a potent neurotoxicant. As cadmium is considered an important environmental contaminant, its neurotoxic potentials to humans may be of concern for the general population (especially elderly) living in areas known for historical cadmium pollution.

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REFERENCES

Ali MM, Shukla GS, Srivastava RS, Mathur N, Chandra SV. Effects of vitamin E on cadmium-induced locomotor dysfunction in rats. *Vet Hum Toxicol* 1993; 35:109-111

Arvidson B, Tjälve H. Distribution of ^{109}Cd in the nervous system of rats after intravenous injection. Acta *Neuropathol (Berl)* 1986; 69:111-116

Baader EW. Chronic cadmium poisoning. *Ind Med Surg* 1952; 21:427-430

Babitch JA. Cadmium neurotoxicity. In: *Metal Neurotoxicity*. Bondy SC, Prasad KN, eds. Boca Raton: CRC Press, Inc., 1988; 141-166

Bar-Sela S, Levy M, Westin JB, Laster R, Richter ED. Medical findings in nickel-cadmium battery workers. *Isr J Med Sci* 1992; 28:578-583

Blum LW, Mandel S, Ducket S. Peripheral neuropathy and cadmium toxicity. *Penn Med* 1989; 92:54-56

Davis JM, Svendsgaard DJ. Nerve conduction velocities and lead: a critical review and meta-analysis. In: *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea MI, Johnson BL, Anger WK, Durao A, Xintaras C, editors. Lewis Publishers, 1990; 353-376

Dunphy B. Acute occupational cadmium poisoning. A critical review of the literature. *J Occup Med* 1967; 9:22-26.

Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. *Ann Neurol* 1991; 10:222-226

Ellis KJ, Vartsky D, Zanzi I, Cohn SH. Cadmium: *In vivo* measurements in smokers and nonsmokers. *Science* 1979; 205:323-325

EPA. Environmental Criteria and Assessment Office. Health document for cadmium. Pub. No. EPA-600/8-79-003. US Environmental Protection Agency, Washington D.C., 1979

Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA. A practical Two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diab Care* 1994; 17:1281-1289

Gabbiani G, Gregory A, Baic D. Cadmium induced selective lesions of sensory ganglia. *J Neuropathol Exp Neurol* 1967; 26:498-506

Hosmer DW, Lemeshow S. Applied logistic regression. New York, John Wiley and Sons, Inc., 1989

Jacobs JM. Blood-brain and blood-nerve barriers and their relationships to neurotoxicity. In: *Principles of Neurotoxicity*. Chang LW, ed. New York: Marcel Dekker Inc., 1994; pp 35-68

Knezevic W, Bajada S. Peripheral autonomic surface potential: a quantitative technique for recording sympathetic conduction in man. *J Neurol Sci* 1985; 67:239-251

Lauwerys R. Cadmium in man. In: *The Chemistry, Biochemistry and Biology of Cadmium*. Webb M, ed. Amsterdam, Elsivier/North-Holland Biomedical Press, 1979; 433-455

Lauwerys RR, Roels H, Buchet JP, Bernard A, Stanescu D. Investigations on the lung and kidney function in workers exposed to cadmium. *Env Health Persp* 1979; 28:137-145

Lin KP, Kwan SY, Chen SY, Chen SS, Yeung KB, Chia LG, Wu ZA. Generalized polyneuropathy in Taiwan: an etiological survey. *Neuroepidemiol* 1993; 12:257-261

McLeod JG, Tuck RR, Pollard JD, Cameron J, Walsh JC. Chronic polyneuropathy of undetermined cause. *J Neurol Neurosurg Psych* 1984; 47:530-535

Musiol A, Szyrocka-Szwed K, Wojczuk J, Kudybka A. Evaluation of the neurological state and EEG investigations in workers with occupational exposure to cadmium. *Wiad Lek* 1981; 34:1615-1620

Nagymajtényi L, Schulz H, Dési I. Behavioural and functional neurotoxicological changes caused by cadmium in a three-generational study in rats. *Hum Exp*

Toxicol 1997; 16:691-699

NIOSH. Criteria for a recommended standard for cadmium. Center for disease control USDHEW, PHS, 1976; Publ. No. (NIOSH)76-192

Oh SJ. Clinical electromyography: nerve conduction studies. Second edition. Baltimore: Williams and Wilkins; 1993

Pal R, Nath R, Gill KD. Lipid peroxidation and antioxidant defense enzymes in various regions of adult rat brain after co-exposure to cadmium and ethanol. *Pharmacol Toxicol* 1993; 73:209-214

Prodan L. Cadmium poisoning: I. The history of cadmium poisoning and uses of cadmium. *J Ind Hygiene* 1932; 14:132-158

Roels HA, Buchet JP, Lauwerys RR, Bruaux P, Clayes-Thoreau F, Lafontaine A, Van Overschelde J, Verduyn G. Lead and cadmium absorption among children near a non-ferrous metal plant. A follow-up study of a test case. *Environ Res* 1978; 15:290-308

Roels HA, Lauwerys RR, Buchet JP, Bernard A, Chettle DR, Harvey TC, Al-Haddad IK. *In vivo* measurement of liver and kidney cadmium in workers exposed to this metal: Its significance with resepect to cadmium in blood and urine. *Environ Res* 1981; 26:217-240

Roels HA, Lauwerys RR, Buchet JP, Bernard A, Vos A, Oversteyns M. Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. *Br J Ind Med* 1991; 48:365-374

Roels HA, Lauwerys RR, Buchet JP, Bernard AM, Vos A, Oversteyns M. Health significance of cadmium induced renal dysfunction: a five year follow up. *Br J Ind Med* 1989; 46:755-764

Sato K, Iwamasa T, Tsuru T, Takeuchi T. An ultrastructural study of chronic cadmium chloride induced neuropathy. *Acta Neuropathol (Berl)* 1978; 41:185-190

Swash M, Schwartz MS. Neuromuscular diseases. A practical approach to diagnosis and managment. Second edition. Berlin: Springer-Verlag; 1988

Valk GD, Nauta JJP, Strijers RLM, Bertelsmann FW. Clinical examination versus neurophysiological examination in the diagnosis of diabetes polyneuropathy. *Diab Med* 1992; 9:716-721

Veves A, Sarnow MR. Diagnosis, classification and treatment of diabetic peripheral polyneuropathy. *Clin Pod Med Sur* 1995; 12:19-30

WHO (International Programme on Chemical Safety): "Cadmium". *Environmental Health Criteria* 134, Geneva, WHO, 1992